Thyroidal Dysfunction and Environmental Chemicals—Potential Impact on Brain Development

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Certain polyhalogenated aromatic hydrocarbons such as polychlorinated biphenyls (PCBs) and dibenzo-*p*-dioxins (dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin) have been shown to have neurotoxic effects and to alter thyroid function during critical periods of thyroid hormone-dependent brain development. This has led to the suggestion that some of the neurotoxic effects of these compounds could be mediated through the thyroid system. Thyroid hormones are essential for normal brain development during a critical period beginning *in utero* and extending through the first 2 years postpartum. They regulate neuronal proliferation, migration, and differentiation in discrete regions of the brain during definitive time periods. Even transient disruption of this normal pattern can impair brain development. Thyroid hormones are necessary for normal cytoskeletal assembly and stability and the cytoskeletal system is essential for migration and neuronal outgrowth. In addition, they regulate development of cholinergic and dopaminergic systems serving the cerebral cortex and hippocampus. Animals perinatally exposed to certain environmental organohalogens such as many of the PCBs and dioxins have abnormal thyroid function and neurologic impairment. Although there are both species and congener variabilities, most reports show exposure results in thyroid enlargement and reduced serum T_4 levels with normal T_3 levels. Initial research concentrated on studying the direct actions of xenobiotics on the thyroid; however, some of these compounds bear a structural resemblance to the natural thyroid hormones and have high affinity with thyroid hormone-binding proteins such as transthyretin. These compounds could act as agonists or antagonists for receptors of the thyroid/steroid/retinoic acid superfamily. These structurally similar organohalogens could act at multiple points to alter thyroid hormone action. The similarity of the neurologic impairment seen in thyroid disorders to that seen following PCB or dioxin exposure suggests that one mechanism of neurotoxicity of these compounds could involve interaction with the thyroid system. *Key words*: brain development, dioxin, organohalogens, polychlorinated biphenyls, thyroid function. — *Environ Health Perspect* 108(suppl 3):433–438 (2000). *http://ehpnet1.niehs.nih.gov/docs/2000/suppl-3/433-438porterfield/abstract.html*

Thyroid hormones are essential for normal brain development in animals and humans and either excess or deficient hormone levels produce significant neurologic impairment if abnormal exposure to environmental chemicals occurs during specific developmental windows. The relationship between polyhalogenated biphenyls and neurologic function is complex. Prenatal exposure to specific biphenyls has been associated with abnormalities in neurologic function. Because toxicant exposure can alter brain thyroid hormone availability and the effects of toxicant exposure frequently resemble those of prenatal hypothyroidism (*1*), there is a need to establish more definitive relationships between toxicant exposure and neurologic function. The complexity of the developing nervous system makes this a difficult task. Because many of these toxicants can produce neurotoxicity independently of any action on the thyroid system, it is important that both those actions mediated independently of the thyroid, perhaps through the aryl hydrocarbon (Ah) receptor, and those mediated through the thyroid system be defined. This requires further research at the cellular and molecular levels. These studies are complicated by the fact that transport of either hormones or the toxicants into brain is complex and involves multiple pathways with multiple potential regulatory points.

Development of the Thyroid

The thyroid, pituitary, and hypothalamus begin development early in gestation (*2*). Thyroid hormone synthesis begins at 10–12 weeks gestation (*3*), and serum thyroid hormone levels rise progressively throughout the remainder of gestation (*4*). The hypothalamic–pituitary–thyroid axis is functional by the latter half of gestation, and maturation continues until approximately 2 months postpartum in humans (*5*). Ligand-bound thyroid hormone receptors are seen by 10 weeks gestation in humans (*6*).

The Role of Thyroid Hormones in Nervous System Development

Thyroid hormones are important regulators of brain development during the fetal and neonatal periods. They control neuronal and glial proliferation in definitive brain regions and regulate neuronal migration and differentiation. Differentiation includes the development of neuronal connectivity and myelination. Because neurologic development occurs in discrete developmental windows, the role of thyroid hormones in orchestrating the timing of specific developmental events and signals is crucial and even transient disorders in thyroid hormone availability can have profound effects on brain development.

Endemic Cretinism

The most severe neurologic impairment resulting from a thyroid deficiency is in endemic cretinism caused by iodine deficiency. In fact, iodine deficiency represents the single most preventable cause of neurologic impairment and cerebral palsy in the world today (*7,8*). These individuals suffer from hypothyroidism that begins at conception because the dietary iodine deficiency prevents synthesis of normal levels of thyroid hormones. It is more severe than that seen in congenital hypothyroidism because the deficiency occurs much earlier in development and results in decreased brain thyroid hormone exposure both before and after the time the fetal thyroid begins functioning. Problems with endemic cretins include mental retardation that can be profound, spastic dysplasia, and problems with gross and fine motor control resulting from damage to both the pyramidal and the extrapyramidal systems. These problems include disturbances of gait, and in the more extreme forms, the individuals cannot walk or stand (*8–10*). If postnatal hypothyroidism is present, there is growth retardation and delayed or absent sexual maturation (*3*). Damage occurs both to structures such as the corticospinal system that develop relatively early in the fetus and structures such as the cerebellum that develop predominantly in the late fetal and early neonatal period. The damage is inversely related to maternal serum thyroxine (T_4) levels but not to triiodothyronine (T_3) levels (*3,8,11*). Delong (*12*) suggests that the neurologic damage occurs primarily in the second trimester, which is an important period for

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formation of the cerebral cortex, the extrapyramidal system, and the cochlea, areas damaged in endemic cretins. Maternal T_3 levels are often normal and the mother therefore may not show any overt symptoms of hypothyroidism. Early development of the auditory system appears to be dependent upon thyroid hormones (*13*). The greater impairment characterized by endemic cretinism relative to congenital hypothyroidism is thought to result from the longer period of exposure of the developing brain to hypothyroidism in endemic cretinism (*3,7,8*).

Congenital Hypothyroidism

Untreated congenital hypothyroidism (sporadic cretinism) produces neurologic deficits having predominantly postnatal origins. Although mental retardation can occur, it typically is not as severe as that seen in neurologic cretinism. Untreated infants with severe congenital hypothyroidism can lose 3–5 IQ points per month if untreated during the first 6–12 months of life (*14*). If the children are treated with thyroid hormones soon after birth, the more severe effects of thyroid deficiency are alleviated. However, these children are still at risk for mild learning disabilities. They may show subtle language, neuromotor, and cognitive impairment (*15*). They are more likely to show attention deficit hyperactivity disorder (ADHD), have problems with speech and interpretation of the spoken word, have poorer fine motor coordination, and have problems with spatial perception (*16*). The severity of these effects is correlated with the retardation of bone ossification seen at birth. This would suggest that the damage is correlated with the mild hypothyroidism they experience *in utero*. Rovet and Ehrlich (*17*) have proposed that the sensitive periods for thyroid hormones vary for verbal and nonverbal skills. The critical period for verbal and memory skills appears to be in the first 2 months postpartum, whereas for visuospatial or visuomotor skills it is prenatal.

Thyroid hormone deficiency impairs learning and memory, which depend on the structural integrity of the hippocampus. Maturation and synaptic development of the pyramidal cells of the hippocampus are particularly sensitive to thyroid hormone deficiency during fetal/perinatal development (*18*). Early in fetal development (rats), thyroid hormone deficiency decreases radial glial cell maturation and therefore impairs cellular migration (*19*), which can lead to irreversible changes in the neuronal population and connectivity in this region. Animals with experimentally induced congenital hypothyroidism show delayed and decreased axonal and dendritic arborization in the cerebral cortex, a decrease in nerve terminals, delayed myelination, abnormal cochlear development, and impaired middle ear ossicle development (*3*).

Resistance to Thyroid Hormones

Resistance to thyroid hormones (RTH) is a genetic disorder typically resulting from a point mutation of the gene producing the thyroid hormone beta receptor (TRβ). The presence of the mutant gene can exert a dominant negative effect on thyroid hormone receptor alpha (TRα)-directed transactivation (*20*). People with RTH commonly show neurologic deficiencies that include a higher incidence of auditory deficiencies and a relatively high incidence of ADHD (*21*). This impairment has been confirmed through behavioral testing and magnetic resonance imaging of the sylvian fissure show discrete structural abnormalities in the cerebral cortex (*22*). The latter damage would most likely result from a deficient action of thyroid hormones *in utero* and the early postnatal period.

Data from Animals

If pregnant rats are treated with the goitrogen propylthiouracil (PTU) early in pregnancy, it delays neuronal proliferation in both the motor and the mesencephalic nuclei of the trigeminal nerve. These neurons normally form relatively early in gestation at a period that would correspond to the first half of gestation in humans (*23*). Eventually these neurons are produced, but the timing of neuronal birth, migration, and synaptogenesis is finely tuned and if neurons are not formed at the appropriate time, they may never reach the right cell layer of the brain and form normal neuronal synapses. Disorganization of the cellular layers of the cerebellar cortex has been shown to occur in postnatal hypothyroidism in rats (*24*). The cellular changes reported by Narayanan and Narayanan (*23*) are reflected in behavioral effects. The trigeminal nerve is important for suckling and the PTU-treated pups had difficulty suckling. Rat fetuses exposed to slightly lower brain thyroid hormone levels *in utero* have problems with learning and memory and are hyperactive as adults, even though thyroid hormone levels are normal as adults (*25*) (Figure 1).

Neurite Outgrowth and Cellular Migration

Thyroid hormone deficiency during a critical developmental period can impair cellular migration and development of neuronal networks. Neuronal outgrowth and cellular migration are dependent on normal microtubule synthesis and assembly and these latter processes are regulated by thyroid hormones (*26*). During cerebral development, postmitotic neurons forming near the ventricular surface must migrate long distances to reach their final destination in the cortical plate where they form a highly organized 6-layer cortical structure. Appropriate timing of this migration is essential if normal connectivity is to be established. This migration depends not only upon specialized cells such as the radial glial cells that form a scaffolding system but also on specific adhesion molecules in the extracellular matrix that are associated with the focal contacts linking migrating neurons with radial glial fibers (*27*). These neurons migrate along radial glial fibers, and following neuronal migration, the radial glial cells often degenerate or become astrocytes (*28*). Migration also depends on adhesive interactions involving extracellular matrix proteins such as laminin and the cell-surface receptor integrin. Laminin is synthesized by astrocytes and bound to the astrocyte surface by the transmembrane receptors integrin and the integrins are held in place by the intracellular

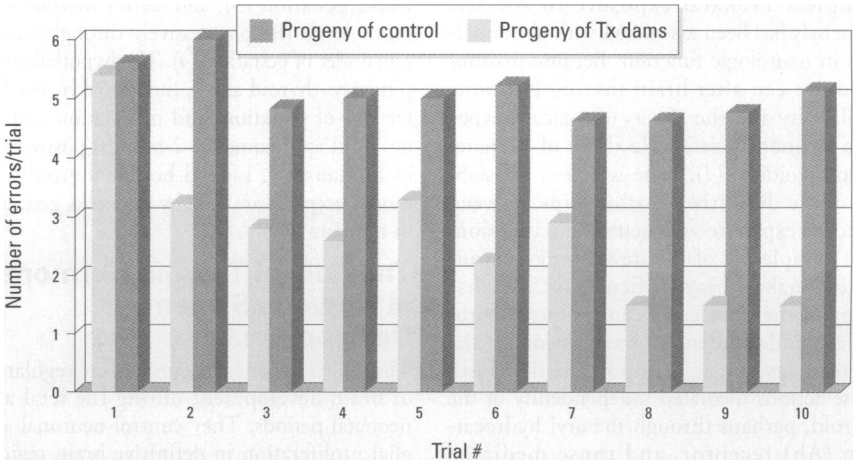

Figure 1. Errors in a Lashley Maze by progeny of hypothyroid (Tx) rats versus progeny of control rats. The progeny of Tx dams are exposed to low levels of thyroid hormones during most of fetal development. While the control progeny learn the maze over 10 trials (trials 2–10 < 1; 4–10 < 2; 8–10 < 3; $p = 0.05$), the progeny of Tx dams never learn the maze during that period. Data from Hendrich et al. (*25*).

astrocyte microfilament network. These macromolecular complexes are called focal contacts and provide directional clues for elongating neurons. T_4 regulates focal contact formation by astrocytes by promoting actin polymerization (*26,29*). T_4 but not T_3 regulates the appearance and regional distribution of laminin in the developing rat cerebellum (*30*), as well as the microfilament network associated with integrins, and T_4 but not T_3 directly alters neurite outgrowth and neuronal migration on laminin in cerebellar explants. Disorders of neuronal migration are considered to be major causes of both gross and subtle brain abnormalities (*28*). Hypothyroidism during fetal and neonatal development results in delayed neuronal differentiation and decreased neuronal connectivity (*26*).

Synaptogenesis and Myelinogenesis

Thyroid hormones regulate development of certain cholinergic and dopaminergic neurotransmitter systems (*31,32*). The cholinergic fibers projecting from the hippocampus to the basal forebrain, including the striatum, are particularly sensitive to thyroid hormone deficiency (*32*). These cholinergic fibers are important in memory and learning, and a well-functioning cholinergic system is a prerequisite for performance on spatial learning tasks in rodents (*33*). This cholinergic system has also been proposed as a site for damage in ADHD). These brain regions (hippocampus, basal forebrain) have particularly high levels of thyroid hormone receptors during development and are sites where thyroid hormones regulate nerve growth factor (NGF) production (*34–36*). Thyroid hormones and NGF cooperate in the development of specific cholinergic systems in the central nervous system (*37*), and thyroid hormones could regulate neurotransmitter development through their action on NGF production in these specific regions. Hypothyroidism decreases choline acetyltransferase (ChAT) quantities in brain regions innervated by these neurons (*32*) because thyroid hormones serve as positive regulatory factors for the ChAT gene (*38*). This drop in ChAT quantity is preceded by a drop in nerve growth factor receptor (NGFR) levels, suggesting that thyroid hormone actions could be mediated by its action on NGFR production (*32*). The development of both dopaminergic and cholinergic systems is delayed in hypothyroidism (*39*). In addition, T_3 regulates expression of the neuron-specific gene for synapsin I, an important protein regulating neurotransmitter release and synaptic plasticity (*40*). Gliogenesis is delayed as is myelination in hypothyroidism (*3,26*). In this case, the impairment represents a developmental delay rather than a block.

Sources of Brain Thyroid Hormones

Thyroid hormone synthesis does not begin until 10–12 weeks of gestation in humans and 17 days of gestation in the rat (*3*). While many important aspects of brain development occur either before the time of fetal thyroid hormone synthesis or at least before synthesis of high levels of fetal hormone, thyroid hormones are available from the mother during early gestation (*3,7*). Thyroid hormones are present in small quantities in rat and human fetal tissue at the earliest ages that it is feasible to measure tissue hormone levels (*3,41*). These low levels of maternal thyroid hormones might be important for developmental events such as cerebral and brain-stem neurogenesis that occur relatively early in development. The importance of maternal thyroid hormones in fetal brain development is seen in the recently published data of Haddow et al. (*42*), showing that maternal thyroid deficiency during pregnancy can impair subsequent neuropsychologic development in children. Later in gestation, both maternal and fetal thyroid hormones are important for fetal brain development. At the time of birth, as much as 17.5% of the thyroid hormones found in the newborn are of maternal origin in rats (*43*) and maternal thyroid hormones can produce neonatal thyroid hormone levels approaching the low normal level in congenitally hypothyroid children with a complete inability to synthesize thyroglobulin and therefore thyroid hormones (*44*).

How Do Thyroid Hormones Reach the Brain?

Thyroid hormones enter the brain through two routes. The predominant route is via the blood–brain barrier involving direct transport through the capillary endothelium and into the brain cells. Hormone transport via this route depends on the serum hormone levels (influenced by serum protein-binding relationships), the transport systems through the endothelium, and the transport systems into the brain cells. The second and less significant route is via the choroid plexus–cerebrospinal fluid (CSF). The thyroid hormone-binding protein transthyretin (TTR) binds T_4 but not T_3. It is produced by the choroid plexus and secreted into the CSF. The TTR then binds to T_4 that enters CSF through the choroid plexus and may play an important role in T_4 transport to the brain cells. Hydroxylated PCBs have a stronger binding affinity for TTR than even T_4 and therefore the presence of these PCBs could compete with T_4 for transport on TTR. In addition, the transport systems for thyroid hormones across cell membranes involve saturable, stereospecific carrier-mediated transport systems (*45,46*). It is possible that these structurally similar toxicants could also compete with thyroid hormones for transport across cell membranes. Although the T_3 has the higher affinity for the thyroid hormone nuclear receptor, T_4 is the predominant form transported into brain. Most of the brain intracellular T_3 pool is derived from local deiodination of T_4 to T_3 by the enzyme iodothyronine 5′-deiodinase (type II).

Development of Thyroid Hormone Receptors

Thyroid hormone receptor binding is present in both the fetal rat brain by 13 days of gestation and the fetal human brain by 10 weeks of gestation (*6,47*). Fetal thyroid hormone secretion begins at 17 days postconception in rats and 8–10 weeks in humans (*3,47*). The fetal rat brain contains predominantly TRα1 and TRα2. While small quantities of TRβ1 are expressed early in gestation in specific regions such as the fetal rat otic vesicles (the precursor to the cochlea) (*13*), most TRβ1 expression occurs late in gestation and the rise in expression corresponds with the rise in fetal/neonatal T_4 secretion (*47*). The highest concentrations of T_3-binding sites in the adult brain are found in the hippocampus, amygdala, and the cerebral cortex, regions of the brain known to be particularly sensitive to thyroid hormone action (*31*).

Thyroid Hormone Action

Thyroid hormone receptors are transcription factors requiring interactions with multiple proteins to regulate gene expression. There are at least three functional thyroid hormone receptors formed from two gene transcripts, TRα1, TRβ1, and TRβ2. The TRα2 isotype does not bind ligand. However, the presence of the TRα2 isotype is thought to inhibit gene regulation mediated through the other isotypes (*20*). Recent data from TRα and TRβ null transgenic mice suggest that functions regulated by one receptor type can at least partially be compensated for by the other receptor type (*48*).

Work is currently under way characterizing the respective roles of the α and β receptor types. Studies of this nature are complicated by the fact that mutant forms of the gene can exert a dominant negative effect on functions of the other gene, thereby magnifying the severity of the deficiency (*20*). Thyroid hormone receptors, unlike steroid receptors, do not require ligand to bind to the receptor. In fact, the unliganded alpha receptor present in early fetal development may be an important inhibitor of transcription of certain thyroid hormone-regulated genes. Thyroid hormone receptors dimerize, and they can either form a homodimer with another thyroid hormone receptor or they can form a heterodimer with

proteins such as the retinoic acid receptor or retinoid X receptor. The ability of thyroid hormones to turn on or turn off a specific gene is controlled by various proteins acting as corepressors or coactivators. The thyroid hormone receptor is a member of the thyroid hormone–retinoic acid–steroid hormone receptor superfamily and as such shows considerable homology with the retinoic acid and the steroid hormone receptors. Excess retinoic acid can act as a neurologic teratogen.

Thyroid hormones regulate gene expression of a limited number of genes. Genes regulated by thyroid hormones in brain include purkinje cell protein, myelin basic protein, nerve growth factor 1-A, NADH dehydrogenase subunit 3, and rat cortex clone 3 (RC3) (neurogranin or calbindin) (*37,49–52*). The gene for the phosphocreatine kinase C substrate RC3 is the only gene shown to be regulated by thyroid hormones in the adult, as well as the fetal brain (*47*). These other genes are developmentally regulated in brain.

Although thyroid hormones have extensive effects on brain development both *in vivo* and *in vitro*, only a few genes appear to be directly regulated by thyroid hormones. This disparity could result from multiple potential factors. It is possible that there are intervening factors regulating thyroid hormone-controlled brain development. These could include the potential impact of other hormones, growth factors, or transcription factors. Thyroid hormones are thought by many to be capable of having both genomic and nongenomic actions. Perhaps some of the actions of thyroid hormones on brain development involve nongenomic actions. Farwell and Leonard (*53*) have shown that thyroid hormone regulation of glial type II iodothyronine 5′-deiodinase, the enzyme converting T_4 to T_3, results from a direct action of T_4 on cellular actin filaments.

PCBs as Hormonally Active Compounds

Certain PCBs and chlorinated dibenzo-*p*-dioxin congeners are structurally similar to the active thyroid hormones (*54*). These structural similarities could theoretically lead to endocrine disruption if the compounds act as agonists or antagonists to the naturally occurring hormone. These compounds include many of the 209 congeners of PCBs and many of the 75 possible congeners of the dioxins. Maier et al. (*55*) have demonstrated that the *ortho*-substituted PCB congeners are more neuroactive than the non-*ortho*-substituted congeners and those compounds with lateral halogen substitution exert many of their biologic actions by acting through the Ah receptor. In addition, there are multiple possible mechanisms of action of these compounds on the thyroid system. These compounds are structurally similar to thyroid hormones and therefore have the potential of binding to proteins that characteristically bind thyroid hormones such as the serum-binding proteins or the thyroid hormone receptor. Laterally substituted chlorinated aromatic compounds such as the *meta* and *para* PCBs, particularly when hydroxylated, are ideally suited to serve as binding ligands for T_4-binding proteins (*54,56*). Because environmental persistence is correlated with lateral substitution, many of the congeners accumulating in the environment are likely to impact the thyroidal system (*55*).

Actions of Organohalogens on the Thyroid

These organohalogens could have direct toxic effects on the thyroid, as suggested by the observed histologic changes reported in the glands of animals exposed to certain PCB and 2,3,7,8-TCDDcongeners that are suggestive of the histologic changes occurring in Hashimoto's thyroiditis in humans (*57*). These histologic changes are often associated with normal or high serum thyroid-stimulating hormone (TSH) levels with low serum T_4 levels (*58*), suggesting a primary thyroidal disorder. Morse et al., (*59*) have shown that maternal exposure to Aroclor 1254 significantly decreases fetal and neonatal plasma T_4 levels in a dose-dependent manner and decreases forebrain and cerebellar T_4 concentrations in fetal rats on day 20. The predominant metabolite accumulating in fetal plasma and forebrain was the hydroxylated congener 2,3,3′,4′,5-pentachloro-4-biphenylol. The hydroxylated congeners of PCBs have a high affinity for TTR (*1,56,60–62*). Cheek et al. (*62*) have shown that half the hydroxylated PCBs they tested had higher affinities than did T_4 for TTR. Only two of the hydroxylated PCBs bound thyroxine-binding globulin, the major transport protein in humans. Only the hydroxylated PCBs inhibited T_3 binding to TRβ; binding affinity was less than 1/10,000 that of T_4 (*65*). The lower serum T_4 levels in PCB-exposed rats could probably result in part from increased metabolism of thyroid hormones. PCB exposure of perinatal rats (*61*) and adult rats (*63*) increases biliary excretion of T_4 by inducing the enzyme T_4-uridine diphosphoglucuronyltransferase, thereby increasing hepatic T_4 glucuronidation (*1*).

Neurologic Effects of Organohalogens

In many species, including humans, perinatal exposure to certain PCB and dioxin congeners can produce neurologic impairment. Children in Taiwan accidentally exposed prenatally to high levels of PCBs (Yu-Cheng, "oil disease") tended to have impaired cognitive development, with these children at 4–5 years of age scoring an average of approximately 5 points lower than unexposed children on the Stanford-Binet test (*64*). Because most of these children were not breast fed, their predominant exposure occurred *in utero*. Jacobson and Jacobson (*65*) have followed the children of a cohort of women who had eaten the equivalent of at least 11.8 kg of PCB-contaminated Lake Michigan fish during the 6-year period prior to giving birth. Prenatal exposure of these children to PCBs was associated with lower full-scale and verbal IQ scores, with the strongest effects seen on short-term and long-term memory and focused and sustained attention. Verbal skills and reading comprehension were impaired. Even though more PCB exposure occurs during lactation than *in utero*, the deficits were associated with prenatal not lactational exposure, suggesting the greatest vulnerability to PCB toxicity of the developing brain occurs *in utero*.

Rodents exposed *in utero* to PCBs have impaired active avoidance acquisition, hyperactivity, and impaired discrimination learning (*1,66*). Hyperactivity in mice following fetal exposure to the congener 3,3′,4,4′-tetrachlorobiphenyl has been attributed to decreased levels of dopamine and dopamine receptor in strial synapses (*67*). Schantz and Bowman (*68*) and Schantz et al. (*69*) have shown that monkeys perinatally exposed to PCBs have problems with learning and memory (*70*). Rat pups exposed to PCBs show delayed development of negative geotaxis, auditory startle, and righting reflexes (*66*), developmental problems were also noted in congenitally hypothyroid rats (*71*). Mice pups exposed to PCBs *in utero* show hyperactivity, and the increased activity is correlated with decreases in dopamine and dopamine-binding sites in the caudate nuclei as well as long-lasting changes in the development of striatal synapses (*66*). The striatum is highly sensitive to the actions of thyroid hormones (*72*).

The developing auditory system is known to be sensitive to thyroid hormones, and hearing disorders including deaf mutism are common in endemic cretinism, with less severe auditory disturbances occurring in congenital hypothyroidism (*73*). In addition, an increased incidence of sensorineural deafness has been noted in RTH (*74*). Bradley et al. (*13*) have shown a correlation between neurologic deafness and expression of Trβ1 and Trβ2 in the region of the embryonic ear (ventral otocyst) giving rise to the cochlea. When Long-Evans rats are given Aroclor 1254 during gestation through lactation, the pups (through day 30 postpartum) had low serum T_4 levels and permanent auditory deficits that most likely resulted from impaired cochlear

development (*75*). In turn, rats given the goitrogen PTU during this same period had similar auditory deficits, the severity of which correlates with the decreased thyroid hormone secretion (*76*).

PCBs and Neurotransmitters

Alterations in neurotransmitter levels in discrete brain regions have been associated with behavioral problems. Both thyroid hormones and certain organohalogens such as some of the PCB congeners and dioxins alter biogenic amines in regions of the brain such as the basal forebrain and hippocampus that are associated with learning and memory. Rat pups exposed *in utero* to *ortho*-substituted but not coplanar PCB congeners have lower-than-normal dopamine levels in the basal forebrain in a manner analogous to what occurs in hypothyroidism (*1,77*). Rat pups either prenatally or lactationally exposed to PCBs have low ChAT activity in the hippocampus and basal forebrain (*78*). The results are the same as those seen in neonatally hypothyroid rats. Because PCB exposure lowered serum T_4 levels, Juarez et al. (*78*) treated some of the pups with T_4 or T_3 and found that T_4, but not T_3, returned ChAT activity almost to control levels, thereby suggesting that PCB-induced ChAT suppression could be mediated through the thyroidal system.

Summary

Polychlorinated biphenyls and dioxins exert their neurotoxic effects through multiple mechanisms. The classical mechanism is through interactions with the Ah receptor. In addition, many of the congeners of PCBs and dioxins alter thyroid function. Because thyroid hormones are essential for normal brain development, it is possible that the xenobiotics could produce neurotoxicity indirectly by altering thyroid-regulated brain development. Many of the neurotoxic effects of organohalogens reported in humans and experimental animals resemble those seen in fetal/neonatal hypothyroidism. Because brain development occurs in very discrete windows, transient exposure of the developing brain to either abnormal thyroid hormone levels or to excessive organohalogens could potentially have lasting neurologic effects. Potential mechanisms of neurotoxicity that could be induced by organohalogens acting through the thyroidal system include the following: *a*) The toxicants could alter thyroid hormone synthesis and secretion, either by acting directly on the thyroid gland or through acting on the pituitary or hypothalamic control of TSH secretion. *b*) The toxicants could compete with thyroid hormone for serum-binding proteins, thereby potentially impairing tissue hormone delivery. *c*) The toxicants could compete with thyroid hormones for membrane carrier systems and therefore inhibit tissue uptake of the hormones. *d*) The toxicants could be either agonists or antagonists for thyroid hormone receptor binding. *e*) The toxicants could alter production of proteins such as coactivators or corepressors that regulate transcription of thyroid hormone-regulated genes. This field remains a fertile area for further investigation.

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